

In the Specification:

Please replace the paragraph beginning at page 6, line 6 with the following:

A1
--Figure 1. Preliminary CLASP-3 cDNA sequence (SEQ ID NO:7; amino acid sequence = SEQ ID NO:8). Notable protein motifs are labeled above the nucleotide sequence.--

Please replace the paragraph beginning at page 6, line 20 with the following:

A2
Fig 2
--Figure 3. A. Amino acid sequence of human and rat CLASP proteins. Sequences were aligned using ClustalW. One letter amino acid abbreviation used. Protein motifs are found within the labeled boxes. A “-” indicates gaps that are placed to acquire a best overall alignment. Other abbreviations: “HC2A” Human CLASP-2 sequence (SEQ ID NO:9), “KIAA” KIAA1058 sequence (SEQ ID NO:10) (Genbank Accession No. AB028981), “rat” TRG gene (SEQ ID NO:11) (Genbank Accession No. X68101), “HC4” Human CLASP-4 sequence (SEQ ID NO:12), “HC1” Human CLASP-1 sequence (SEQ ID NO:13), “HC3” Human CLASP-3 sequence (SEQ ID NO:14), “HC5” Human CLASP-5 sequence (SEQ ID NO:15). B. Alignment of DOCK motifs found within the human CLASPs (SEQ ID NOS:16-20, 24, 25, 27-31, 35, 37-43, 47 and 49-55) and rat TRG (SEQ ID NOS:26, 36 and 48) and compared to canonical DOCK motifs (SEQ ID NOS:21-23, 32-34, 44-46 and 56-58). Consensus amino acids found within all DOCK motifs are also indicated.--

Please replace the paragraph beginning at page 6, line 30 with the following:

A3
--Figure 4. A. Nucleotide (SEQ ID NO:59) and predicted amino acid sequence (SEQ ID NO:60) of CLASP-3 cDNA. Notable protein motifs are indicated. Additionally, boundaries between exons and introns are indicated by arrows. These boundaries were defined by sequencing Bacterial Artificial Chromosomes containing genomic DNA corresponding to CLASP-3 (BACs). BACs were sequenced using primers derived from exon sequences corresponding to the CLASP-3 cDNA (SEQ ID NOS:61-81). Each exon/intron boundary is noted (as “Ref” with an appropriate reference number) above the cDNA sequence. The References contain exact nucleotide location of introns. The names and nucleotide numbers of the primers that were used in sequence

Cont
A3
reactions are also indicated. All nucleotide numbers refer to CLASP-3 cDNA sequence. As shown in the Reference, not all of the sequence from sequencing reactions produced sequence matching the cDNA. These nucleotide sequences that did not match the exon sequence for CLASP-3 were considered to be intron sequences. **B.** Alignment of human (SEQ ID NOS:9, 10 and 12-15) and rat (SEQ ID NO:11) CLASP amino acid sequences by ClustalW. Notable protein motifs are indicated. Additionally, the exon/intron borders described in part A are indicated with hand-drawn vertical lines between appropriate amino acids. Reference numbers are indicated in the right margin and correspond to References in part A.--

Please replace the paragraph beginning at page 8, line 14 with the following:

A4
ab
b2
--**Figure 7.** Sequence of human CLASP-3 exons and introns, and potential promoter. A. Sequence of human CLASP-3 exons and intron borders (SEQ ID NOS:82-97). Stretches of noncontiguous genomic sequence from the Human Genome Project (GENBANK entry gi9212047) were aligned using the human CLASP-3 cDNA as a template and Sequencher sequence analysis software (Gene Codes Corp). 15 exons representing approximately the 5' 10% of the human CLASP-3 cDNA sequence are presented in predicted 5' to 3' order. Exon sequences are underlined and are flanked by intron sequence. This exon/intron map could only have been produced having the isolated human CLASP-3 cDNA. Nucleotide numbers for each exon and flanking intron sequences are indicated and represent the annotation found in Genbank entry gi9212047. Note that these sequences and numbers are with respect to the reverse complement (anti-parallel) of the nucleotides in Genbank entry gi9212047. **B.** Genomic nucleotide sequence (SEQ ID NO:98) upstream of the human CLASP-3 5' terminus, which represents the putative promoter region for human CLASP-3. The first exon of the CLASP-3 cDNA is underlined. Nucleotides 58000 to 60348 of the reverse complement of gi9212047 are shown.--

Please replace the paragraph beginning at page 8, line 29 with the following:

AS
ab
b3
--**Figure 8.** Amino acid alignment and comparison between the human (h) CLASP family members (SEQ ID NOS:99-104). Amino acid sequences were aligned using ClustalW. The alignment is presented in order of their greatest pairwise similarity scores. Single letter amino acid

Brat A5
abbreviations are used. Asterisks indicate complete identity, while colons and periods indicate sequence similarity among CLASP family members. Dashes indicate gaps inserted in the amino acid sequence to facilitate alignment. Labelled boxes are domains with similarity to known protein motifs; unlabelled boxes represent regions of similarity between all CLASPs and may represent CLASP-specific domains.--

Please replace the paragraph beginning at page 22, line 2 with the following:

A6
--The CLASP-3 extracellular domain is characterized by one cadherin EC-like motif (Pigott, R. and Power, C., 1993, *The Adhesion Molecule Factbook*. Academic Press, pg. 6; Jackson, R. M. and Russell, R. B., 2000, *J. Mol. Biol.* 296: 325-34). Several highly conserved cysteines are found in the extracellular domain, as well as various glycosylation signals. Through its extracellular domains, CLASP-3 may interact with ligands in a homotypic and/or heterotypic manner to establish the immunological synapse in conjunction with molecules such as TCR, MHC class I, MHC class II, CD3 complex and accessory molecules such as CD4, CD3, ICAM-1, LFA-1, and others. Many cadherins contain a pro-domain of approximately 50 to 150 amino acids that is removed before localization to the plasma membrane. This cleavage is presumed to be carried out by Furin (Posthaus, H. *et al.*, 1998, *FEBS Lett* 438: 306-10) at a consensus sequence of RKQR (SEQ ID NO:126). Furin is a protease that is at least partially responsible for the maturation of certain cadherins. CLASP-3 has the sequence RCSR (SEQ ID NO:127) at nucleotides 431 through 442 as shown in FIG. 1 (nucleotides 3097 through 3108 of FIG. 6). By homology, this region is around 120 amino acids after the predicted protein start site for hCLASP-3 indicated in FIG. 1 (1032 amino acids after the predicted protein start site for hCLASP-3 indicated in FIG. 6). This region may be a pro-domain and cleavage may be required for CLASP-3 function, or aspects of CLASP-3 function--

Please replace the paragraph (**Table 1**) beginning at page 24, line 5 with the following:

A7

--Table 1
CLASP-3 ITAM Motifs

Motif No.	Sequence Motif	SEQ ID NO:
1	YXXV-X ₃ -YXXXL	128
2	YXXV-X ₂ -YXXXK	129
3	YXXI-X ₅ -YXXT	130

Please replace the paragraph beginning at page 25, line 6 with the following:

A8

--CLASP-3 polypeptides contain a new "DOCK" motif, not previously described in the scientific literature. The CLASP DOCK motif includes a series of five tyrosines surrounded by conserved sequences in regions A, B, C, D, and G (see FIG. 3B). There are also two highly conserved non-tyrosine containing regions (E and F) separated by 20 amino acids (P+EXAI+X+; SEQ ID NO:131) and (LX(M/L)XL+GX(V/I)XXXVNNG; SEQ ID NO:132) (where X is any amino acid).--

Please replace the paragraph beginning at page 55, line 9 with the following:

A9

--In one embodiment, the antisense sequence is complementary to relatively accessible sequences of the CLASP-3 mRNA (e.g., relatively devoid of secondary structure). This can be determined by analyzing predicted RNA secondary structures using, for example, the MFOLD program (Genetics Computer Group, Madison WI) and testing in vitro or in vivo as is known in the art. Another useful method for identifying effective antisense compositions uses combinatorial arrays of oligonucleotides (see, e.g., Milner *et al.*, 1997, Nature Biotechnology 15: 537). Examples of oligonucleotides that can be tested in cells for antisense suppression of CLASP-3 function are those capable of hybridizing to (*i.e.*, substantially complementary to) CLASP-3 at the following positions:

GfA

Oligo	Sequence 5' - 3'	length	notes/comments
1	CTATTACTAACGGCTTC GAGAACGATTAA (SEQ ID NO:133)	28-mer	spans nucleotides 6-33 of the sequence of FIG. 1 (nucleotides 2672-2699 of FIG. 6)
2	CTGGAAAACGACTTT CCTTGGAGCCTCAAG (SEQ ID NO:134)	31-mer	spans nucleotides 419-449 of the sequence of FIG. 1 (nucleotides 3085-3115 of FIG. 6), and is complementary to the region encoding the cadherin cleavage site
3	GTGCTGCTGAGTGGAC TAGACACTGTGCAGC (SEQ ID NO:135)	31-mer	spans nucleotides 2426-2465 of the sequence of FIG. 1 (nucleotides 5089-5119 of FIG. 6., and is complementary to the region encoding the transmembrane domain

Please replace the paragraph beginning at page 56, line 6 with the following:

A10 --The antisense nucleic acids (DNA, RNA, modified, analogues, and the like) can be made using any suitable method for producing a nucleic acid, such as the chemical synthesis and recombinant methods disclosed herein. In one embodiment, for example, antisense RNA molecules of the invention can be prepared by de novo chemical synthesis or by cloning. For example, an antisense RNA that hybridizes to CLASP-3 mRNA can be made by inserting (ligating) an CLASP-3 DNA sequence (e.g., SEQ ID NO:1, or fragment thereof) in reverse orientation operably linked to a promoter in a vector (e.g., plasmid). Provided that the promoter and, preferably termination and polyadenylation signals, are properly positioned, the strand of the inserted sequence corresponding to the noncoding strand will be transcribed and act as an antisense oligonucleotide of the invention. The term "operably linked" refers to a functional linkage between a nucleic acid expression control sequence (such as a promoter or enhancer) and a second nucleic acid sequence, wherein the expression control sequence directs transcription of the nucleic acid corresponding to the second sequence.--

Please replace the paragraph (Primer Table) beginning at page 110, line 18 with the following:

All
--Primer Table

CLASP gene	Sense Primer	Sense sequence	Sense SEQ ID NO:	Antisense Primer	Antisense sequence	Antisense SEQ ID NO:
CLASP-7	HC7gS5	AGGCCTTGTCTCTGTTA CCTG	136	HC7gAS1	TGTCATGTACTGCACTCGCA CAGC	137
CLASP-7	HC7gS3	ACAGGAACCTGCTGTAC GTGTAC	138	HC7AS14	TCGTGGCTGCACAGGATGCG GGTG	139
CLASP-4	C4P2	GACCCATTAGGAGGTCT AC	140	HC4AS3'	CGGGATCCATTGTCACCGTA CATCTGC	141
CLASP-4	C4P2	GACCCATTAGGAGGTCT AC	140	HC4AS3'	CGGGATCCATTGTCACCGTA CATCTGC	141
CLASP-1	hC1S5'	TATGTCTCAGTCACCTAC CTG	142	HC1AS3'Kpn	CTTGGTACCACTTCAGCACT AGATGAGATG	143
CLASP-1	C1S7	TCAAGACCAGGGCATGC AAG	144	HC1AS3'Kpn	CTTGGTACCACTTCAGCACT AGATGAGATG	143

All
Please replace the paragraph beginning at page 111, line 1 with the following:

A12
--In-frame stop codons were not present suggesting that the cDNA was not full length. To obtain the 5' terminus of CLASP-3, 5' RACE was employed. Antisense oligonucleotides directed against the 5' end of the longest CLASP-3 sequence were generated:

Primers used for human CLASP-3 5' RACE

Primer sequence(5' to 3')

nucleotide position

HC3RACE5 (SEQ ID NO:145)

AAAAAACATCTGGGAAGGATAAGTGATAG 1016-1044

HC3RACE6 (SEQ ID NO:146)

ATTGCTGATCTGCCAGGGTAGTAATGG 983-1010

HC3RACE7 (SEQ ID NO:147)

*Cont
AV2*

TGCGGGAAACTCTAAGATTCTCTGGTAG 1643-1671

HC3RACE8 (SEQ ID NO:148)

TTCAC TTGAAGCACGTCCGGAGTTAGGC 1589-1616--

Please insert the accompanying paper copy of the Sequence Listing, page numbers 1 to 142, at the end of the application.

REMARKS

The amendment to the paragraph beginning at page 25, line 6 amends the "DOCK" motif peptide sequences in line 10 and the motif labels in line 9. This is supported by the two motifs found in FIG. 3B. These amino acid motifs presently found on line 10, i.e., (P+EXAI+XM) and (LXML+GXVXXXVNNG), which are presented in FIG. 3B, boxes E and F, on the two lines labeled "CONSENSUS", appear as:

P+E AI+ M

+

and

L M L+G V VN G

L I,

respectively. The "+" symbol and the letters "L" and "I" on the second "CONSENSUS" line indicate optional amino acid variants at these indicated positions occur in their homology comparison. Therefore, the terminal "M" residue in the first motif (motif E) has been amended to a "+" symbol to reflect these variants. The two positions in the second motif (motif F) have also indicated these optional amino acid variants by the "M/L" and "V/I" designations. The Sequence Listing has incorporated the indicated optional variants into their respective positions.

The amendment includes amending the letters to which those highly conserved non-tyrosine containing regions refer. The first amino acid motif is presented in FIG. 3B, page 1 of 2, where the last region boxed is labeled region E. This region is followed by a boxed region labeled "F" in FIG. 3B, page 2 of 2, instead of region "G" as designated on page 25, line 9.

This amendment further corrects the number of amino acid residues stated to be separating these two motif sequences in line 10. Although the number of amino acid residues between boxes E and F is stated to be nine on line 10 of the Specification (illustrated in FIG 3B as